RHEUMATIC FEVER AS A COLLAGEN DISEASE*

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(RECEIVED FOR PUBLICATION SEPTEMBER 23, 1954)

Rheumatic fever is typical of the collagen diseases in that lesions of mesenchyme, heart, blood vessels, joints, and serous membranes are frequently associated with hyperglobulinaemia, lymphadenopathy, and splenomegaly. Not only is the disease typical but it occurs more frequently and, being a prepubertal disease, is less complex than most of the diseases of the group. There are, therefore, several clues to its aetiology. These clues provide evidence by analogy as to the nature of collagen diseases in general.

Haemolytic Streptococci.—Group A haemolytic streptococci are the most important factor in the pathogenesis of rheumatic fever. There is no simple bacteria-host relationship that can be defined in terms of Koch's postulates. It is the host, not the streptococcus, that decides the issue, for few patients with haemolytic streptococcal infection develop the disease. The syndrome occurs when recurrent attacks of haemolytic streptococcal tonsillitis have led to marked localization of the infection, a high level of antibodies, and frequently minimal constitutional disturbance until the development of rheumatic fever. The disease is part of what Rantz and others (1946) have termed "the post-streptococcal state". This state is always associated with hypersensitivity (of the tuberculin type) to streptococcal allergens; in the guinea-pig, at least, cells damaged by a specific streptococcal toxin are more susceptible to bacterial allergens than cells not so damaged, and this may in part explain the particular role of the streptococcus (Grey and Long, 1954). But the full rheumatic syndrome does not necessarily occur in all patients exhibiting sensitivity to streptococcal allergens.

Nutritional Factors

Essential Aminoacids.—It has been suggested that, of the many agents that influence susceptibility (Waksman, 1949), nutritional and hormonal factors are the most important (Long, 1954), and that, in particular, a deficiency in essential sulphur containing aminoacids is in part responsible for increased susceptibility to the disease. In support of this hypothesis is the fact that essential aminoacids cannot be stored and therefore a deficiency is readily induced. Rheumatic fever is less common in the protein-eating farming states than in the cotton and tobacco states of America (Peete, 1944). Egg consumption is lower in children who develop rheumatic fever than in those who do not (Wallis, 1954). Powdered egg yolk prevented recurrence of rheumatic fever in underprivileged children in spite of recurrent attacks of haemolytic streptococcal infection (Coburn and Moore, 1943). It is noteworthy that hyperglobulinaemia and multiple small areas of cardiac necrosis have been described in conditions attributed to a deficiency of animal protein (Davies, 1952), and that of all sources of protein, egg protein has the highest biological value (Block and Mitchell, 1946). Gamma globulin can be synthesized extrahepatically even when a deficiency of essential aminoacids has impaired hepatic synthesis of albumin. Whipple and others (1942) showed that although the body cannot store protein, there are large reserves in tissues which can be withdrawn without impairing vital function. Plasma proteins are readily replaced from tissues; conversely, plasma proteins injected intravenously can supply all the protein requirements of the body, suggesting that plasma protein can be readily incorporated into tissues. Neuberger and his colleagues (Harkness and others, 1954) have shown in the rat that protein electrophoretically indistinguishable from plasma protein is present, probably extra-cellularly, in large amounts in close association with the collagenous protein of connective tissue. It has been suggested that in the collagen diseases in general, and rheumatic fever in particular, connective tissue provides protein and globulin for the general metabolic pool (Long, 1954), this loss being associated with characteristic degenerative changes in mesenchyme.

* Read at the Third International Congress of Internal Medicine in Stockholm on September 16, 1954.

Humphrey and McFarlane (1954) have recently shown that gamma globulin provides aminoacids for incorporation into liver cells. It is possible that under conditions of protein deficiency hyperglobulinaemia represents a compensatory phenomenon to increase the supply of aminoacids to the liver.

Ascorbic Acid.—Large amounts of ascorbic acid are needed to saturate and to maintain saturation in patients with rheumatic fever, with rheumatoid arthritis, and with active tuberculosis. It is possible that such patients oxidize ascorbic acid more readily than other patients and that this hypothesis might, through the intermediary glutathione, be linked with a deficiency of sulphur-containing aminoacids (Long, 1954).

Hormonal Factors

Of the various hormones, insulin and cortisone provide the most important clues.

Insulin.—Rheumatic fever seldom occurs in diabetics (Barach, 1926; Joslin, 1937); the development of diabetes in rheumatic patients reduces the incidence of heart damage (Joslin, 1937). Conversely, patients with rheumatic fever show "functional hyperinsulinism" (Steincrohn, 1938; Abrahamson, 1944). The symptoms of rheumatoid arthritis are relieved during the compensatory phase that succeeds insulin hypoglycaemia (Kersley and others, 1951). Two further facts are noteworthy: insulin and glutathione are closely related (Houssay, 1950), and the islets of Langerhans alone among the endocrine glands obtain their nerve supply from the parasympathetic.

Cortisone.—This relieves the symptoms of rheumatic fever and of many of the collagen diseases. The nerve supply of the adrenal cortex is from the sympathetic. Cortisone antagonizes many of the actions of insulin. It transfers aminoacids from carcase to liver, a phenomenon frequently associated with a reversion of hyperglobulinaemia to normal levels. It is possible that by this means cortisone makes good a deficiency in the liver of essential aminoacids and so removes the stimulus that induces hyperglobulinaemia. Again, the biological activity of cortisone is closely linked with the metabolism of glutathione (Long, 1954).

Conclusions

Rheumatic fever occurs in patients with marked hypersensitivity (of the tuberculin type) to streptococcal allergens. Eggs, and probably biologically valuable protein, decrease susceptibility to the disease. Hyperinsulinism increases, and hypoinsulinism decreases, susceptibility. Cortisone decreases susceptibility. Ascorbic acid requirements are increased. The common factor relating hypersensitivity to these nutritional and hormonal agents is the metabolism of sulphur-containing aminoacids and of glutathione.

These ideas have been criticized for being too complex. "The best hypotheses are the simplest. All current theories about the aetiology of rheumatic fever are complicated, and none more so than that recently suggested by Long" (Annotation, 1954). Of course, of any two hypotheses, either of which will

TABLE

ANALOGY BETWEEN RHEUMATIC FEVER IN MAN AND THE B.C.G.-INFECTED GUINEA-PIG*

Lines of Inquiry		Man (Rheumatic fever)	Guinea-pig (B.C.G.-infected)
Bacterial Allergy (Tuberculin type)		+	+
Ascorbic-acid Synthesis		−	−
Cortisone	1. General resistance	+	+
	2. Particular resistance {Gamma-globulin synthesis	+	+
	2. Particular resistance {Antitoxin synthesis	+	+
	3. Anti-allergic action	+	+
	4. Anti-inflammatory action	−?	−
	5. Specificity of molecule	+	+
Insulin	Diabetogenic agents	↓	↓
	Antidiabetogenic agents	↑	↑
Thyroid	Hyperthyroidism	↑	↑
	Hypothyroidism	↑	↑
–SH (Reduced glutathione)		?	↑
Anti –SH		?	↓

↓ Decrease susceptibility ↑ Increase susceptibility * For detailed argument see Long (1954).

explain all the facts, the simpler is to be preferred. But what simple hypothesis will unite bacterial, allergic, nutritional, and hormonal hypotheses, or explain the analogy between the tuberculin sensitive guinea-pig and rheumatic fever? (Table). By considering a single facet of the problem and ignoring the rest, a simple hypothesis can be produced, but this is at the cost of seeking simplicity where none exists.

Rheumatic fever, though complex, is the collagen disease of which we know most; I have selected clues which can be followed and which may lead to a fuller understanding of the group as a whole.

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Rhumatisme articulaire aigu comme maladie collagène

RÉSUMÉ

Le rhumatisme articulaire aigu survient chez des personnes douées d'une hypersensibilité marquée (type de tuberculine) aux allergènes streptococciques. Des oeufs et probablement des protéines biologiquement utiles réduisent la susceptibilité à cette maladie. De même l'hypoinsulinisme la réduit tandis que l'hyperinsulinisme l'accentue. La cortisone réduit la susceptibilité. La demande d'acide ascorbique se trouve augmentée. Comme facteur commun entre l'hypersensibilité et les agents nutritifs et hormonaux mentionnés on trouve le métabolisme des aminoacides contenant du soufre et celui du glutathione.

Le rhumatisme articulaire aigu, bien que complexe, est une des maladies collagènes que nous connaissons mieux; j'ai indiqué les pistes à suivre pouvant mener au meilleur entendement de l'entier groupe morbide.

Reumatismo poliarticular agudo como enfermedad colagena

SUMARIO

El reumatismo poliarticular agudo ocurre en personas con hipersensibilidad marcada (tipo de tuberculina) a los alérgenos estreptocóccicos. Huevos y probablemente proteinas biológicamente útiles reducen la susceptibilidad a esta enfermedad. Asimismo el hipoinsulinismo la reduce mientras que el hiperinsulinismo la aumenta. La cortisona reduce la susceptibilidad. La demanda de ácido ascórbico se ve aumentada. Como factor común entre la hipersensibilidad y los agentes nutritivos y hormonales mencionados encuéntrase el metabolismo de los aminoácidos que contienen azufre y la glutatión.

El reumatismo poliarticular agudo, aunque complejo, es la enfermedad colagena que conocemos mejor; he indicado aquí pistas que pueden llevar a la mejor comprensión del grupo mórbido entero.